Question 1

A 65-year-old man with a two-year history of mild angina presents to the emergency department after 30 minutes of severe chest pain following unaccustomed heavy physical activity. He has taken three glyceryl trinitrate tablets without relief. The pain is relieved by oxygen. Over the preceding six months, he has been stable on atenolol 50 mg/day, aspirin and isosorbide mononitrate 60 mg/day, he has only experienced angina twice, and has not used his glyceryl trinitrate over this period.

The most likely explanation for the failure of the glyceryl trinitrate to relieve his angina is:

A. Poor absorption due to dry mouth
B. Onset of unstable angina
C. Reduced drug potency
D. Nitrate tolerance
E. Paroxysmal atrial fibrillation

Answer C

From mims

Anginine is a vasodilator which relieves angina pectoris. Pain in angina pectoris is believed to be the result of myocardial ischaemia secondary to coronary artery disease. In the relief of acute anginal pain the effect is apparent after two to three minutes and lasts for up to 20 or 30 minutes.

Pharmacology. Anginine redistributes blood blow along collateral channels and from epicardial to endocardial regions and thus may increase blood flow to ischaemic areas. Anginine also reduces oxygen demand by increasing venous capacitance causing pooling of blood in the peripheral veins and thereby reducing ventricular volume. Furthermore, the fall in arterial pressure will also reduce myocardial oxygen demand, although this may be offset by a reflex tachycardia. The beneficial effects of nitrates in pulmonary oedema depend on venous dilation and reduction of preload. Anginine causes coronary vasodilation in coronary arteries that are in spasm, and may relieve pain in variant angina by this mechanism.

Anginine is thought to exert its vasodilator effect through the activation of guanylate cyclase in vascular smooth muscle cells by nitric oxide. This results in an increased synthesis of cyclic guanosine monophosphate, which leads to smooth muscle relaxation.

Pharmacokinetics. Glyceryl trinitrate is readily absorbed through the buccal mucosa but is rapidly metabolised so it has a fleeting duration of action.

Peak plasma levels of glyceryl trinitrate given sublingually appear within four minutes.

Distribution. Glyceryl trinitrate has a volume of distribution of about 3 L/kg. It is taken up by vascular smooth muscle cells.

Metabolism. In smooth muscle cells the nitrate group is cleaved to inorganic nitrite and then to nitric oxide (thought to be responsible for glyceryl trinitrate’s vasodilatatory effect). Glyceryl trinitrate also undergoes hydrolysis in plasma and is rapidly hydrolysed in the liver by glutathione organic nitrate reductase to dinitrates and mononitrates. At least half of the intact glyceryl trinitrate is cleared from the blood in one to three minutes.

Excretion. The main urinary metabolite of glyceryl trinitrate is the mononitrate.

Anginine should be stored in a cool place. It should not be carried close to the body and should be kept out of direct sunlight.

An unopened bottle has a shelf life of two years if stored below 25 deg. C. However, tablets unused three months after first opening a bottle should be discarded and a fresh supply obtained.